REMARKS

Claims 1-21 are pending in the application. Claims 17-21 have been withdrawn as directed to non-elected subject matter.

Claim Rejections Under 35 U.S.C. § 102

Claim 14 is rejected under 35 U.S.C. § 102 (e) as being anticipated by Wohlstadter *et al* (Pub. No.: US 2004/00864233 A1). Applicants respectfully traverse.

Applicants' invention is directed in part to a circuit board biosensor apparatus wherein the apparatus comprises reference electrodes (see, for example, page 6, lines 25-30; page 7, lines 22-34; page 20, lines 22-33 through to page 21, lines 1-2; page 22, lines 21-34 through to page 24 lines 1-21; page 28, lines 7-33 through to page 29, lines 1-7; Examples 4.1 - 5.13); a plurality of nucleic acids attached thereto (see, for example, page 8, lines 13-29; page 10, lines 8-33; page 18, lines 19-33 through to page 20, lines 1- 15; page 21, lines 19-33 through to page 24, lines 1-26; page 26, lines 11- 32 through to page 27, lines 1-19; Examples 4.1-5.13); a means for measuring current (see, for example, page 7, lines 12-21; page 11, lines 1-15; page 18, lines 7-18; page 19, lines 29-33 through to page 20, lines 1-2; page 22, lines 9-20; page 27, lines 20-33 through to page 29, lines 1-7). The current is produced by the hybridized electrode bound nucleic acid segments and nucleic acid target sequences when an electric potential is applied.

Applicants also teach a pulse amperometric monitor for the electrochemical detection of nucleic acid sequences (Claims 4, 6 and dependent claims therefrom). See, for example, Figures 5, 6, 7-10, 12, and 15-18 showing data obtained with a pulse amperometric monitor and the text of the instant application on page 21, lines 2-33 through to page 22, lines 1-34. Also described is an amperometric monitor for the electrochemical detection of nucleic acid sequences that comprise pulse and intermittent pulse modes of operation. See for example, page 51, lines 1-33 through to page 56, lines 1-15; Figure 7 shows the nature of the varied modes of applying potential to the sensors.

In contrast to Applicants invention, Wohlstadter *et al.*, does not teach or disclose a biosensor. The patterned arrays in Wohlstadter *et al.*, are exclusively used for stimulating and detecting luminescence of analytes, and thus does not constitute a biosensor. Unlike a biosensor array, the patterned arrays of Wohlstadter et al. electrical stimulation ca be used to excite labeled molecules and result in light emission. Wohlstadter *et al.* do not teach altering the potential of an electrode to detect target nucleic acids specifically and selectively by current produced at the electrode, as taught by Applicants.

Applicants measure the current produced by the capture of a target nucleic acid. That is, the current is target induced and not applied by the apparatus. In other words, the current is produced by the hybridized electrode bound nucleic acid segments and nucleic acid target sequences when an electric potential is applied. Moreover, the small, portable instrument that applies potential to a working electrode is the same instrument that transfers, records, analyzes and/or displays the current generated by the electrochemical assays as taught by applicants. (See for example, page 18, lines 7-18; page 19, lines 1-8; page 28, lines 7-30). Applicants apparatus is also tailored as a small, portable instrument that applies potential to a working electrode is the same instrument that transfers, records, analyzes and/or displays the current generated by the electrochemical assays. (See for example, page 19, lines 1-8).

Furthermore, Wohlstadter *et al.*, do not teach or disclose the use of an electrochemical apparatus for establishing an appropriate potential on an electrode surface so that an electrical current can be generated at the electrode (the sensor) and used for nucleic acid detection. Moreover, only optical signals are referenced and detection requires use of a photon detector, and there is no disclosure of any electrochemical detection of target-dependent currents. Applicants submit that electrochemiluminescence (ECL) for electrically exciting labeled molecules to provide for light emission would require significantly different supports, labels and methods from those taught by Applicants.

In view of the afore going reasons, Applicants submit that Wohlstadter *et al.* do not teach or disclose the instant invention.

In view thereof, Applicants respectfully request reconsideration and withdrawal of the 35 U.S.C. § 102(e) rejection as it applies to claim 14.

Claims 1-11, 13, 14 and 16 are rejected under 35 U.S.C. § 102(e) as being anticipated by Doung *et al.* (US 2002/0177135A1).

Applicants respectfully traverse.

Applicants would like to draw the Examiner's attention that Doung *et al.* is not an appropriate reference, either as a 35 U.S.C. § 102(e) reference or otherwise. The earliest date of Doung *et al.*, is July 27, 1999 which was a provisional application. The Examiner asserts that the instant claims only have priority to the parent filed 4/14/200. If the Examiner deems it helpful, Applicants can file a 37 C.F.R. §1.131 Declaration in order to evidence conception of the invention before the 35 U.S.C. § 102(e) date of these cited references.

Applicant's instant application claims priority to Serial Number 60/040,949 filed March 18, 1997.

However, even if Doung *et al.* was a reference, Doung *et al.* does not teach or disclose the instant invention. Doung *et al.* do not teach methods by which biosensor arrays can be used to detect nucleic acid sequences. For example, Doung *et al.* does not teach how to make measurements of any of the many types of biochips referenced in the text of the patent. The only results presented in the Duong et al Patent (figures 63-65 (simulated data) and 66 and 67 (showing curve fitting of "original data") have no indication of how the mathematical curve-fitting procedures used are applicable are useful in handling data obtained from arrays, and the actual source and nature of the "original data" of Figures 66 and 67 is unknown (even x and y axis of the figure is unclear).

Specifically, the Examiner asserts, on pages 6-7, that:

Doung et al. discloses devices configured to hold multiple cartridges comprising biochips. Said biochips comprise a substrate with at least one surface comprising an array of electrodes, (page 7, paragraph 0067). The devices comprise a number of cartridge stations that are configured to receive the biochips, with different types of biochips allowing different types of components. The stations can include a wide variety of different components, including thermocontrollers, signaling systems, sensors for leak detection, alphanumeric displays, and detectors. Preferred embodiments include the use of biochips comprising electrodes that rely on electrochemical detection, and thus the devices and/or stations can comprise device boards and processors. (Paragraph 0030 and 0065). As will be appreciated by those in the art, the cartridge can comprise a number of components, including reaction chambers, inlet and outlet ports, heating elements including thermoelectric components, RF antennae, electromagnetic components, memory chips, sealing components such as gaskets, electronic components including interconnects, multi plexers, processors, etc. (paragraph 0050). Doung et al. provide methods and compositions for the multiplex analysis of samples and target analytes. Samples (either raw samples or treated samples (e.g. amplified, purified, etc.)) are loaded into the cartridges of the invention, optional caps are put on, and the cartridges loaded into a station of the device. Additional reagents are added as necessary, and assay complexes formed. (Paragraph 0358). Which is viewed to be inclusive of instant claims 13 and 16.

Structure 17 on page 20 shows that said electrodes comprise nucleic acids covalently attached. Said electrodes are used in hybridization assay using ETM labels. And said ETM can be detected electronically by monitoring electron transfer. (see pages 25, 31, 32, 35, 41). And said monitoring can be done via amperometric detection (page 36). This method of detection involves applying a potential. Electron transfer of differing efficiencies is induced in samples in the presence or absence of target nucleic acid; that is the presence or absence of the target nucleic acid and thus the label probe, can result in different currents (paragraph 0371, pages 36-37). Electrodes can be made that have a single species of nucleic acid or multiple nucleic acid species (paragraph 0424). Said devices are also used for quantification (paragraph 0426).

Applicants respectfully disagree. Claim 1 of Doung *et al.* recites: a biochip cartridge comprising a) a reaction chamber comprising: i) a substrate comprising an array of electrodes, each comprising: A) a self-assembled monolayer; and B a capture binding ligand; and II, an inlet port for the introduction of reagents, and interconnects to allow the electrical connection of said

electrodes to a processor. In contrast, Applicants teach measurements with biosensor arrays that are different from the cartridges of Doung et al. Notably, a biosensor array is defined as an array of electrodes configured so that they can detect biomolecules, such as nucleic acids. A biosensor array need not contain a self-assembled monolayer or an inlet port for the introduction of reagents.

Furthermore, Doung *et al.*, is lacking in teaching how biochip arrays could be measured, particularly in regard to electrochemical detection of nucleic acids on biochips. Even in the rather extensive text, no mention is made of the possible use of amperometric measurements in which an interrupted pulse train is used, as in a preferred method of the instant invention, i.e. intermittent pulse amperometry). Even though, electrodes may be connected to a processor and are independently addressable does not teach one how to achieve this connection and individually address the electrodes. Specifically, Doung *et al.*, does not teach or disclose how to avoid cross-talk between electrodes, nor does it describe how to deal with variations between electrodes and generation of non-target-dependent signals. Descriptions of actual operations are also completely absent and Doung et al do not show how to quantify the data.

In contrast, Applicants describe the use of biosensor arrays for enzyme-enhanced amperometric detection of nucleic acids which is not described by Doung *et al.*, and thus the rejected claims are not anticipated or described, nor taught, by Doung *et al.* In particular, Doung et al do not teach or disclose use of enzyme labels to provide an electrochemically detectable product, either on single electrodes or in electrode arrays.

In view thereof, Applicants respectfully request reconsideration and withdrawal of the instant rejection. As such, claims 1-11, 13, 14 and 16 are patentable over the cited references.

Claim Rejections Under 35 U.S.C. § 103

Claims 12 and 15 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Doung *et al.* (US 2002/0177135A1) in view of Stratagene catalog 1988 page 39.

Applicants respectfully traverse.

Doung *et al.*, has been discussed above and for the sake of brevity will not be repeated here. Doung *et al.*, does not teach one of ordinary skill in the art how to use biosensors for nucleic acid detection. The referenced Stratagene catalog does not cure the deficiencies of Doung *et al.* Neither Doung *et al* nor the referenced Stratagene teach or disclose a kit containing both reagents <u>and</u> a biosensor apparatus in which the reagents are used in the biosensor apparatus as taught by Applicants. Nor do the cited references teach or disclose that a sensor and means thereof for the detection of <u>target-dependent electrical currents</u> (<u>not color</u>) generated by <u>targets selectively</u> captured on electrodes. Both cited articles <u>fail</u> to disclose means to generate and detect currents associated with captured nucleic acid targets.

As discussed above, applicants measure the <u>current</u> produced by the <u>capture</u> of a target nucleic acid. That is, the current is <u>target induced</u> and not applied by the apparatus. Moreover, the small, portable instrument that applies potential to a working electrode is the same instrument that transfers, records, analyzes and/or displays the current generated by the electrochemical assays as taught by applicants. (See for example, page 18, lines 7-18; page 19, lines 1-8; page 28, lines 7-30). Applicants apparatus is also tailored as a small, portable instrument that applies potential to a working electrode is the same instrument that transfers, records, analyzes and/or displays the current generated by the electrochemical assays. (See for example, page 19, lines 1-8). Applicants further teach, the material needed to for the electrodes, the nucleic acid sequences, the attachment of the nucleic acid probes to the electrodes, the quantity of capture nucleic acids e.g. number per area (surface of electrode can be as small as 0.001 mm^2 to about 100 mm^2; page 8, lines 4-5), the pattern of nucleic acids on the electrodes, the length of nucleic acid capture sequences, the solutions needed to measure the electric current, especially in view of detection of one nucleic acid sequence difference (see, for example, detection of single nucleotide polymorphisms on page 31, lines 8- 32 through to page 33, lines 1- 28) and the like.

Applicants teach use of a 5'-phosphate modified reverse primer during a PCR step to generate double stranded PCR products that can subsequently be made into single stranded DNA

by digestion with an exonuclease that acts on the 5'-phosphate modified strand. The forward primer used in the PCR may be optionally modified as well, so that the single-stranded material remaining after exonuclease digestion is prepared for a) binding to the sensor surface and b) hybridization with a detector probe that has high selectivity for the nucleic acid target sequence of interest. (see, for example, page 14, lines 7-24; page 30, lines 3-33 through to page 31, lines 1-7).

In summary, Applicants teach measuring the current produced by the capture of a target nucleic acid. That is, the current is target induced and not applied by the apparatus. Neither Doung *et al.*, nor Stratagene alone or in combination teach Applicants invention.

For at least the reasons given above, Applicants respectfully submit that Claims 12 and 15 and dependent claims therefrom are allowable over the cited references of record. Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection.

CONCLUSION

Applicants respectfully request entry of the foregoing remarks and reconsideration and withdrawal of all rejections. It is respectfully submitted that this application with claims 1-16 define patentable subject matter and is in condition for allowance. Accordingly, Applicant respectfully requests allowance of these claims.

This response is being filed within the shortened statutory period and thus believe that no fees are due. Although, Applicants believe that no extensions of time are required with submission of this paper, Applicants request that this submission also be considered as a petition for any extension of time if necessary. The Commissioner for Patents and Trademarks is hereby authorized to charge the amount due for any retroactive extensions of time and any deficiency in any fees due with the filing of this paper or credit any overpayment in any fees paid on the filing or during prosecution of this application to Deposit Account No. 50-0951.

If there are any remaining issues or the Examiner believes that a telephone conversation with the Applicants' attorney would be helpful in expediting prosecution of this application, the Examiner is invited to call the undersigned at telephone number shown below.

Respectfully submitted,

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